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Direct Preparation of Pyrrolizidines using Imines and Isonitriles

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Abstract: An acid mediated annulation reaction for the formation of 7a-substituted unnatural pyrrolizidines is described. To reach this goal, the pyrroline 3-(3,4-dihydro-2*H*-pyrrol-5-yl)propan-1-ol is reacted with a large variety of isonitriles directly resulting in the target compounds. The reaction is operationally simple and tolerates air and water, and the resulting pyrrolizidines can be further transformed to the corresponding oxidized and reduced derivatives.

Key words: Pyrrolizidines; Isonitriles; Cyclizations; Pyrrolines.

Pyrrolizidines constitute a privileged ring structure in alkaloids, with hundreds of natural products employing this motif.[1] The utilization of these bicyclic N–heterocycles in drug discovery has been hampered by their well-known *in vivo* oxidation to the corresponding pyrrole derivatives, which can undergo undesired off-target reactions (Figure 1).[2] One way of preventing this aromatization involves quaternization by the presence of an additional substituent on the 7a-position.

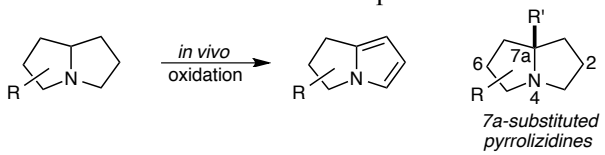


Figure 1. Substitution at the 7a-position in pyrrolizidines prevents oxidation to the pyrrole derivative.

Interestingly, among the many approaches to such heterocycles, there are only few methods reported in the literature to prepare these 7a-substituted pyrrolizidines carboxamides.[3] In the context of our research on natural products as lead structures inducing neurite outgrowth,[4] we discovered a reaction that yields 7a-substituted pyrrolizidines such as **1** from pyrroline **2** and isonitriles **3** (Figure 2). Related structures are the mixed α7-nicotinic receptor antagonist **4**, recently identified by Reymond and coworkers[5], commercially used antiarrhythmic agent pilsicainide **5**[6], and the muscarinic antagonist **6** identified by Suzuki et al.[3b] Compounds such as **1** are regioisomeric towards **4** but are potentially interesting structures for medicinal chemistry and drug discovery. To the best of our knowledge, up to this point, there is no method reported for the direct preparation of pyrrolizidine-7a-carboxamides. For the construction of the pyrrolizidine building block, isonitriles serve as C nucleophiles at the C(7a)-position on a putative pyrrolizidinium intermediate. In this study, we report on a method for the preparation of pyrrolizidine-7a-carboxamides from pyrroline and isonitrile precursors.

Previous work documented in the literature on a series of quinolines and naphthalenes with a 1-azabicyclo[3.3.0]octane moiety required multi-step sequences for their preparation.[3a] Instead of installing an ester on the 7a-position and further peptide coupling, our reaction contains a masked amide functionality by using isonitriles.

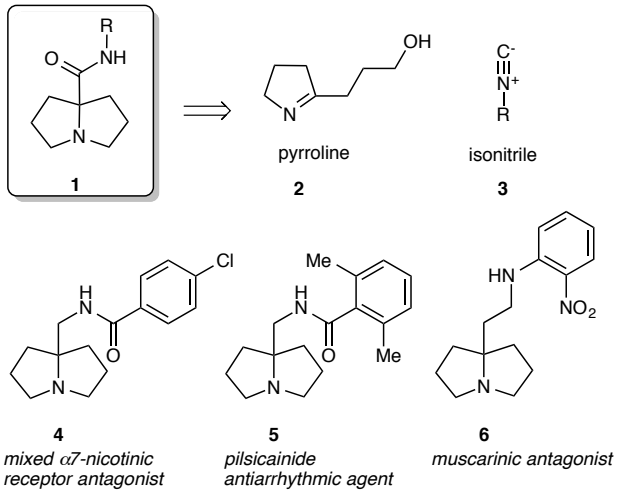
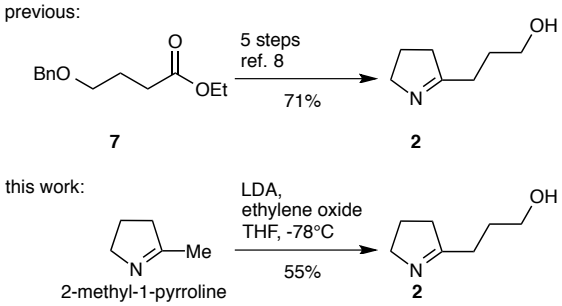


Figure 2. 7a-Substituted pyrrolizidines present lead structures in neuroscience and drug discovery

Isonitriles have been shown to serve as useful building blocks for the synthesis of complex molecular targets especially in multicomponent reactions such as Ugi- or the Passerini reactions.[7] For example, isonitriles have been shown to react with pyrrolines or piperideines and carboxylic acids in an Ugi-3-component reaction to substituted proline or homoproline derivatives.[8] Initial experiments were carried out with pyrroline **2** carrying a primary hydroxyl group in the side chain.

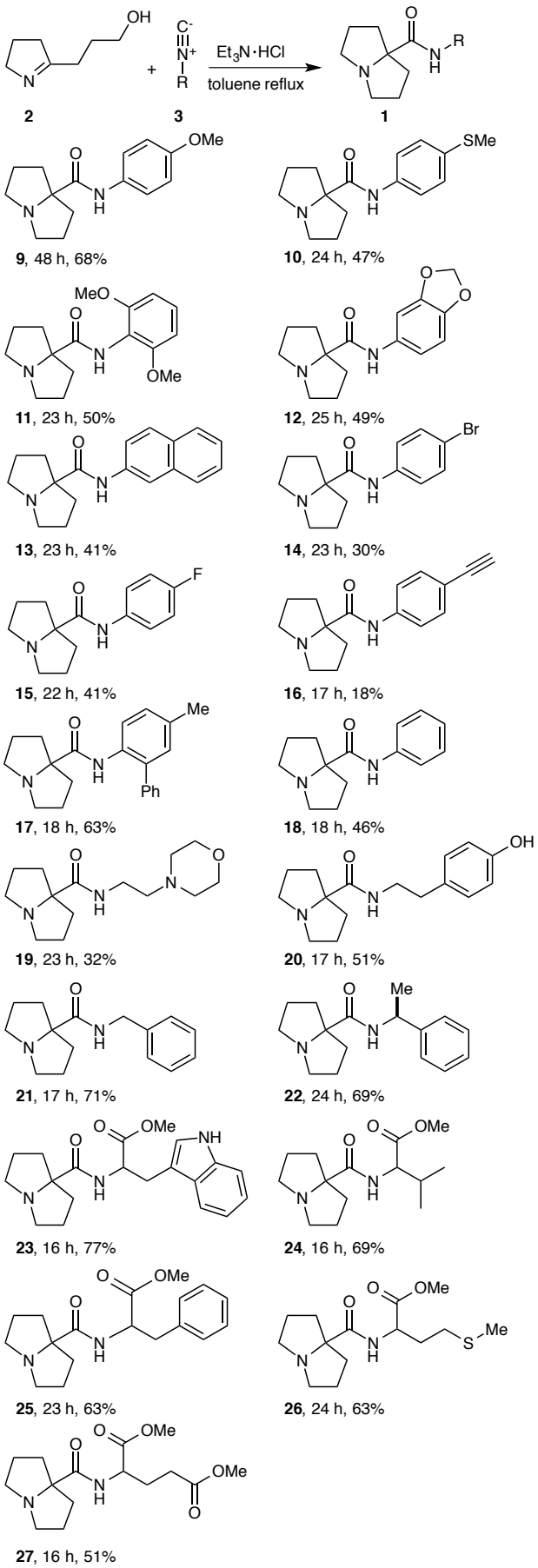


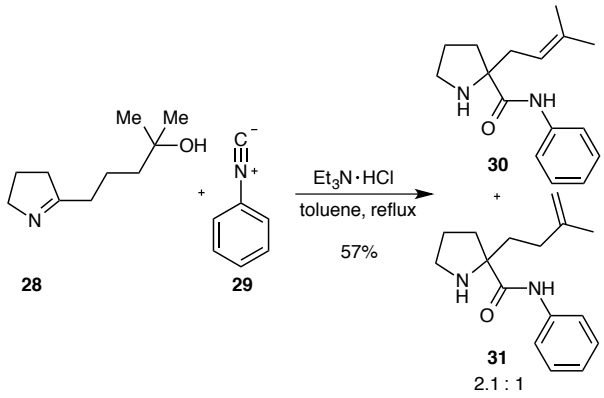
Scheme 1. Preparation of pyrroline **2** from 2-methyl-1-pyrroline and ethylene oxide.

The precursor **2** was previously synthesized[9] via a multi-step procedure from 4-benzyloxybutyric acid ethyl ester **7** (Scheme 1). As an improvement, we were able to di-

rectly react 2-methyl-1-pyrroline with LDA and ethylene oxide to the pyrroline **2** in one step from commercially available starting materials.[10] Initial experiments identified weak Brønsted acids as suitable catalysts for the reaction of pyrroline **2** and isonitriles **3** to deliver pyrrolizidine-7a-carboxamides **1** in acceptable yields. Best results for this transformation were obtained with tertiary amine hydrochloride salts, as secondary ammonium salts as well as pyridinium chloride delivered the product in lower yield. The reaction temperature required rather high boiling solvents from which toluene was identified as optimal reaction medium. After further optimization, the best acid for this transformation turned out to be $Et_3N{\cdot}HCl$.[11] Heating under reflux in toluene was necessary, as at lower temperature no or very little conversion of the starting material was observed. With these optimized conditions in hand, we investigated the scope and limitations of this method. The reaction was found to tolerate a wide scope of substrates (Scheme 2). Aromatic isonitriles resulted in good to moderate yields depending on their electronic properties. The reaction with electron donating isonitriles gave the products **9**, **10**, **11** and **12** in higher yields than rather electron poor isonitriles which delivered the products **13**, **14**, **15** and **16**.[12] Surprisingly, the sterically demanding example **17** was observed in higher yield than product **18** from the reaction with phenyl isonitrile. A reason for this might be the positive inductive effect of the methyl group in the para-, and of the phenyl group in the ortho-position of the aromatic ring. Aliphatic isonitriles were also tolerated in this reaction, albeit at lower yield. For example, compound **19** bearing a morpholine ring was obtained in low yield. In contrast, unprotected phenols such as **20** or benzyl substituted pyrrolizidine-carboxamide **21** could be obtained in good yield. Further, the sterically more demanding α-methylbenzyl isocyanide gave product **22** in lower yield than benzyl isocyanide indicating that steric factors influence the outcome of the reaction to some extent. On average the best yields were obtained using isocyanoacetates which can be easily prepared from the corresponding amino acid esters using a known literature method.[13] In this respect, the highest yield was obtained for the tryptophane related product **23** as well as for valine derivative **24**. Additionally, the reaction towards pyrrolizidine **24** was performed using 10 equivalents of water and product formation was still observed, albeit in lower yield (69% to 45%). Aromatic (to deliver product **25**), as well as aliphatic amino acids containing heteroatoms (to deliver products **26** and **27**) were also reacted in good yields. Unfortunately, these substrates suffered from complete racemization under the reaction conditions as has been observed before for isocyanoacetates due to their α-C-H acidity (pKa = 9-11).[13,14] Complete racemization occurs already on the isonitrile precursors, so that full racemization is observed before product formation. For pyrrolizidine **22**, however, no racemization was observed. Extending this method to pyrroline **28** carrying a tertiary hydroxy group in the side chain, pyrrolidine derivative **30** as a 2.1:1 mixture of prenylated

Scheme 2. Scope of isonitriles for the construction of pyrrolizidine-7a-carboxamides.



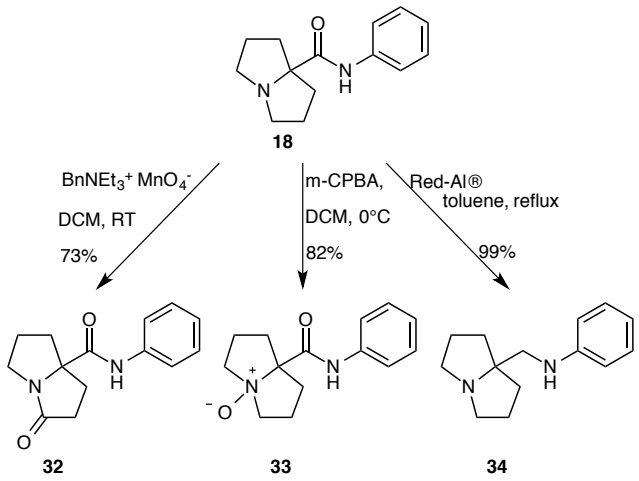


Scheme 3. Formation of pyrrolidines from pyrrolines and isonitriles.

pyrrolidine and its $\Delta^{3,4}$ isomer **31** is obtained instead of pyrrolizidine formation (Scheme 3). Mechanistically, formation of the pyrrolizidine derivatives might proceed via a pyrrolizidinium intermediate.[15] A mechanistic investigation of these reactions is currently underway in our laboratories.

As an extension of this method, we were able to further functionalize the pyrrolizidine core through oxidation on the 3-position with a procedure developed by Schäfer and coworkers using benzyl(triethyl)ammonium permanganate.[16] In this report, the transformation has been applied to simple long-chain alkyl amines as well as *N*,*N*-alkylanilines. A direct oxidation on the 3-position of the pyrrolizidine core has, to the best of our knowledge, not been reported so far. As a mild oxidant, benzyl(triethyl)ammonium permanganate delivers the 3*H*-pyrrolizin-3-one product **32** in good yield, allowing rapid access to these biologically relevant structures.[17] Additionally, the tertiary nitrogen atom can be oxidized with *m*-CPBA to furnish *N*-oxides such as **33**, an important motif of natural products such as the verticillatin alkaloids[18] as these dipoles are also the oxidized product of a self-defense mechanism of certain species against toxic pyrrolizidines.[19] Alternatively, the amide functionality of the pyrrolizidine-7a-carboxamide can be reduced to diamine **34** in quantitative yield.[20] These structures have been identified to show binding affinities for the central muscarinic cholinergic receptor and therefore represent lead structures for the treatment of neurodegenerative diseases.[21]

In summary, a method for the direct preparation of pyrrolizidine-7a-carboxamides from imines and isonitriles has been described. The reaction allows access to these biologically relevant structures using aromatic isonitriles as well as isocyanoacetates. Generally, the reaction with electron rich isonitriles furnished the product in higher yield than with electron deficient precursors. In addition, isocyanoacetates were found to be excellent substrates, although racemization occurred during the reaction. Finally, pyrrolizidine-7a-carboxamides have been shown to be readily transformed by oxidation or reduction. Extension of this method to biologically active compounds such as muscarinic agonists are underway in our laboratories and will be reported in due course.



Scheme 4. Further transformations to biologically active lead structures.

Reactions were performed under argon in oven-dried glassware. Solvents used for chemical transformations were either puriss. quality or dried by filtration through activated aluminum oxide under nitrogen (H_2O content < 10 ppm, *Karl-Fischer* titration). Yields refer to purified, dried and spectroscopically pure compounds. Flash chromatography was performed using silica gel 60 (230-240 mesh) from Fluka or activated basic aluminium oxide (58 Å pore size) from Sigma-Aldrich using a forced flow eluent at 0.1-0.3 bar pressure.

3-(3,4-dihydro-2*H*-pyrrol-5-yl)propan-1-ol (2)

Diisopropylamine (6.12 mL, 43.0 mmol, 1.20 equiv.) was dissolved in anhydrous THF (12 mL) and cooled to -78°C. *n*-BuLi (25 mL of 1.6 mol·L^{-1} solution in hexane, 40.0 mmol, 1.10 equiv.) was added dropwise and stirred for 40 min at -78°C. 2-Methyl-1-pyrroline (3.4 mL, 36.0 mmol, 1.00 equiv.) was added and the reaction mixture was stirred for 1 h at -78°C. Ethylene oxide (16 mL, 40.0 mmol, 2.5 mol·L^{-1} solution in THF) was added at -78°C and the mixture was stirred for 5 h. The reaction was quenched with aqueous sat. $NaHCO_3$ solution and the layers were separated. The aqueous layer was extracted with EtOAc (3x) and the combined organic layers were dried over $MgSO_4$. Evaporation of the solvents gave the crude product as a yellow oil. The residue was purified by distillation (b.p. 55°C, 9.4·10^{-3} mbar) to obtain a colorless oil, which turned yellow upon standing. (2.44 g, 19 mmol, 53% yield). ^{1}H NMR (250 MHz, $CDCl_3$) δ = 3.87–3.75 (m, 2H), 3.73–3.65 (m, 2H), 2.57–2.38 (m, 4H), 1.96–1.82 (m, 4H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 179.57, 63.10, 60.43, 38.31, 32.58, 28.62, 22.68 ppm. FTIR (neat) ν = 2965, 2921, 2854, 1619, 1431, 1303, 1267, 1194, 1113 cm^{-1}. HR-MS (ESI): $C_7H_{14}NO^+$ $[M+H]^+$: calculated: 128.1070 found: 128.1070.

General procedure for the synthesis of pyrrolizidines

Imine **2** (0.47 mmol, 1.00 equiv.) and isonitrile (0.47 mmol, 1.00 equiv.) were dissolved in dry toluene (3.6 mL) and $Et_3N{\cdot}HCl$ (0.94 mmol, 2.00 equiv.) was added. The suspension was heated under reflux and the reaction was monitored by TLC. The reaction mixture was diluted with water, the layers were separated and the aqueous layer was extracted using Et_2O (2x). The combined organic layers were dried over $MgSO_4$. The solvents were removed in vacuo and the residue was purified by flash column chromatography.

_N_-(4-Methoxyphenyl)tetrahydro-1_H_-pyrrolizine-7a(5_H_)-carboxamide (9)

Purification by column chromatography on silica gel using CH_2Cl_2:MeOH = 40:1 (R_f = 0.19). The product was isolated as a yellow solid in 68% yield (83 mg, 0.32 mmol). ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 9.94 (s, 1H), 7.62–7.46 (m, 2H), 6.93–6.79 (m, 2H), 3.79 (s, 3H), 3.24–3.11 (m, 2H), 2.71–2.60 (m, 2H), 2.36–2.24 (m, 2H), 1.91–1.67 (m, 6H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$) δ = 175.65, 156.10, 131.56, 120.81, 114.20, 78.38, 56.01, 55.65, 37.36, 26.39 ppm. FTIR (neat) ν = 3256, 2960, 2869, 1678, 1516, 1245 cm^{-1}. HR-MS (ESI): $C_{15}H_{21}N_2O_2^+$ $[M+H]^+$: calculated: 261.1598 found: 261.1601. M.p. = 84°C.

_N_-(4-(Methylthio)phenyl)tetrahydro-1_H_-pyrrolizine-7a(5_H_)-carboxamide (10)

Purification by column chromatography on basic aluminum oxide using EtOAc:pentane = 1:6 (R_f = 0.32). The product was obtained as a brown oil in 47 % yield (61 mg, 0.22 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.05 (s, 1H), 7.60–7.51 (m, 2H), 7.30–7.20 (m, 2H), 3.17 (ddd, *J* = 10.3, 6.0, 4.6 Hz, 2H), 2.72–2.60 (m, 2H), 2.45 (s, 3H), 2.33–2.24 (m, 2H), 1.90–1.76 (m, 4H), 1.76–1.67 (m, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 176.02, 135.99, 132.90, 128.43, 119.92, 78.47, 56.02, 37.37, 26.38, 17.16 ppm. FTIR (neat) ν = 3245, 2964, 2938, 2868, 1681, 1505 cm^{-1}. HR-MS (ESI): $C_{15}H_{21}N_2OS^+$ $[M+H]^+$: calculated: 277.1369 found: 277.1371.

_N_-(2,6-Dimethoxyphenyl)tetrahydro-1_H_-pyrrolizine-7a(5_H_)-carboxamide (11)

Purification by column chromatography on silica gel using CH_2Cl_2:MeOH = 30:1 (R_f = 0.22). The product was obtained as a yellow oil in 50 % yield (69 mg, 0.24 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.26 (s, 1H), 7.13 (t, *J* = 8.4 Hz, 1H), 6.57 (d, *J* = 8.4 Hz, 2H), 3.80 (s, 6H), 3.21 (dt, *J* = 10.2, 5.2 Hz, 2H), 2.64 (dt, *J* = 9.9, 7.1 Hz, 2H), 2.35 (dt, *J* = 11.6, 5.4 Hz, 2H), 1.92–1.83 (m, 4H), 1.83–1.73 (m, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 176.49, 155.70, 127.19, 115.18, 104.75, 100.11, 78.47, 56.27, 55.97, 37.22, 26.58 ppm. FTIR (neat) ν = 3281, 2959, 2867, 1686, 1593, 1507, 1461, 1256, 1108 cm^{-1}. HRMS (ESI) Exact mass calculated for $C_{16}H_{23}N_2O_3^+$ $[M+H]^+$: calculated: 291.1703 found: 291.1704.

_N_-(Benzo[_d_][1,3]dioxol-5-yl)tetrahydro-1_H_-pyrrolizine-7a(5_H_)-carboxamide (12)

Purification by column chromatography on basic aluminium oxide using EtOAc:pentane = 1:4 (R_f = 0.36). The product was obtained as a brown solid in 49 % yield (63 mg, 0.23 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.97 (s, 1H), 7.36 (d, *J* = 2.1 Hz, 1H), 6.89 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.74 (d, *J* = 8.3 Hz, 1H), 5.93 (s, 2H), 3.16 (ddd, *J* = 10.3, 5.9, 4.5 Hz, 2H), 2.65 (ddd, *J* = 10.0, 7.8, 5.6 Hz, 2H), 2.33–2.23 (m, 2H), 1.90–1.76 (m, 5H), 1.76–1.69 (m, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 175.69, 147.91, 143.87, 132.73, 112.21, 108.14, 101.94, 101.25, 78.41, 56.00, 37.36, 26.39 ppm. FTIR (neat) ν = 3238, 2963, 2870, 1676, 1504, 1038 cm^{-1}. HR-MS (ESI): $C_{15}H_{19}N_2O_3^+$ $[M+H]^+$: calculated: 275.1390 found: 275.1389. M.p. = 106–108°C.

_N_-(Naphthalen-2-yl)tetrahydro-1_H_-pyrrolizine-7a(5_H_)-carboxamide (13)

Purification by column chromatography basic aluminium oxide using EtOAc:pentane = 1:15 (R_f = 0.28). The product was isolated as a brown solid in 41% yield (54 mg, 0.19 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.18 (s, 1H), 8.25 (d, *J* = 2.1 Hz, 1H), 7.71 (dd, *J* = 9.8, 7.4 Hz, 3H), 7.48 (dd, *J* = 8.8, 2.2 Hz, 1H), 7.37 (ddd, *J* = 8.2, 6.8, 1.4 Hz, 1H), 7.33–7.28 (m, 1H), 3.19–3.11 (m, 2H), 2.68–2.57 (m, 2H), 2.32–2.23 (m, 2H), 1.84–1.73 (m, 4H), 1.73–1.66 (m, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 176.34, 135.59, 134.12, 130.59, 127.76, 127.65, 126.49, 124.82, 119.75, 115.76, 78.59, 56.08, 37.43, 26.42 ppm. FTIR (neat) ν = 3237, 3057, 2963, 2867, 1681, 1524, 1496 cm^{-1}. HR-MS (ESI): $C_{18}H_{21}N_2O^+$ $[M+H]^+$: calculated: 281.1648 found: 281.1650. M.p. = 108–110°C.

_N_-(4-Bromophenyl)tetrahydro-1_H_-pyrrolizine-7a(5_H_)-carboxamide (14)

Purification by column chromatography on basic aluminium oxide using EtOAc:pentane = 1:8 (R_f = 0.19). The product was isolated as a brown solid in 30% yield (43 mg, 0.14 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.11 (s, 1H), 7.54–7.50 (m, 2H), 7.44–7.40 (m, 2H), 3.17 (ddd, *J* = 10.3, 6.1, 4.6 Hz, 2H), 2.70–2.62 (m, 2H), 2.32–2.24 (m, 2H), 1.89–1.78 (m, 4H), 1.77–1.69 (m, 2H) ppm.
ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 176.20, 137.23, 131.97, 120.92, 116.37, 78.51, 56.01, 37.36, 26.36. FTIR (neat) ν = 3236, 2965, 2869, 1684, 1503, 1396 cm^{-1}. HR-MS (ESI): $C_{14}H_{18}BrN_2O^+$ $[M+H]^+$: calculated: 309.0597 found: 309.0600. M.p. = 91°C.

_N_-(4-Fluorophenyl)tetrahydro-1_H_-pyrrolizine-7a(5_H_)-carboxamide (15)

Purification by column chromatography on basic aluminium oxide using EtOAc:pentane = 1:8 (R_f = 0.5). The product was isolated as a white solid in 41% yield (48 mg, 0.19 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.06 (s, 1H), 7.64–7.51 (m, 2H), 7.07–6.95 (m, 2H), 3.17 (ddd, *J* = 10.3, 6.1, 4.6 Hz, 2H), 2.66 (ddd, *J* = 9.9, 7.8,

5.4 Hz, 2H), 2.34–2.24 (m, 2H), 1.91–1.78 (m, 4H), 1.78–1.68 (m, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 175.97, 159.2 (d, J_{C-F} = 242.7 Hz), 134.29, 120.95, 120.87, 115.72, 115.50, 78.42, 56.00, 37.35, 26.37 ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ = −122.03 ppm. FTIR (neat) ν = 3230, 2965, 2870, 1680, 1513, 1407, 1211 cm^{-1}. HR-MS (ESI): $C_{14}H_{18}FN_2O^+$ $[M+H]^+$: calculated: 249.1398 found: 249.1399. M.p. = 133-135°C.

_N_-(4-Ethynylphenyl)tetrahydro-1_H_-pyrrolizine-7a(5_H_)-carboxamide (16)

Purification by column chromatography on basic aluminium oxide using Et_2O:pentane = 1:3 (R_f = 0.21). The product was obtained as a brown oil in 18 % yield (22 mg, 0.086 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.17 (s, 1H), 7.63–7.54 (m, 2H), 7.49–7.40 (m, 2H), 3.24–3.12 (m, 2H), 3.03 (s, 1H), 2.71–2.62 (m, 2H), 2.33–2.24 (m, 2H), 1.90–1.78 (m, 4H), 1.78–1.67 (m, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 176.25, 138.58, 133.03, 118.95, 117.22, 83.77, 78.53, 76.62, 56.01, 37.38, 26.36 ppm. FTIR (neat) ν = 3236, 2931, 2869, 1680, 1513 cm^{-1}. HR-MS (ESI): $C_{16}H_{19}N_2O^+$ $[M+H]^+$: calculated: 255.1492 found: 255.1494.

_N_-(5-Methyl-[1,1'-biphenyl]-2-yl)tetrahydro-1_H_-pyrrolizine-7a(5_H_)-carboxamide (17)

Purification by column chromatography on silica gel using CH_2Cl_2:MeOH = 20:1 (R_f = 0.28). The product was obtained as a white solid in 63% yield (88 mg, 0.28 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.24 (s, 1H), 8.27 (d, J = 8.3 Hz, 1H), 7.48–7.41 (m, 2H), 7.41–7.31 (m, 3H), 7.17 (dd, J = 8.3, 2.1 Hz, 1H), 7.06 (d, J = 2.1 Hz, 1H), 2.77–2.66 (m, 2H), 2.42–2.33 (m, 2H), 2.34 (s, 3H), 2.27–2.16 (m, 2H), 1.78–1.52 (m, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 175.74, 139.00, 133.30, 132.89, 132.56, 130.47, 129.43, 128.97, 128.62, 127.53, 120.22, 78.56, 55.47, 37.11, 26.74, 21.01 ppm. FTIR (neat) ν = 3208, 2963, 2868, 1681, 1514, 1467 cm^{-1}. HR-MS (ESI): $C_{21}H_{25}N_2O^+$ $[M+H]^+$: calculated: 321.1961 found: 321.1960. M.p. = 89–91 °C.

_N_-Phenyltetrahydro-1_H_-pyrrolizine-7a(5_H_)-carboxamide (18)

Purification by column chromatography on silica gel using CH_2Cl_2:MeOH 40:1 (R_f = 0.41). The product was obtained as a yellow solid in 46% yield (50 mg, 0.22 mmol). ^{1}H-NMR (500 MHz, $CDCl_3$) δ = 10.07 (s, 1H), 7.61 (dd, J = 8.5, 1.0 Hz, 2H), 7.35– 7.28 (m, 2H), 7.11–7.05 (m, 1H), 3.22–3.13 (m, 2H), 2.71–2.62 (m, 2H), 2.34–2.25 (m, 2H), 1.89–1.78 (m, 4H), 1.78–1.69 (m, 2H) ppm. ^{13}C-NMR (126 MHz, $CDCl_3$) δ = 176.11, 138.15, 129.06, 123.93, 119.31, 78.47, 56.01, 37.37, 26.37 ppm. FTIR (neat) ν = 3187, 2961, 2923, 2853, 1670, 1600, 1510, 1440, 1312 cm^{-1}. HR-MS (ESI): $C_{14}H_{19}N_2O^+$ $[M+H]^+$: calculated: 231.1492 found: 231.1494. M.p.: 105–108°C.

N-(2-Morpholinoethyl)tetrahydro-1H-pyrrolizine-7a(5H)-carboxamide (19)

Purification by column chromatography on basic aluminium oxide using EtOAc (R_f = 0.17). The product was obtained as a colorless oil in 32 % yield (41 mg, 0.15 mmol). ^{1}H NMR (250 MHz, $CDCl_3$) δ = 8.17 (s, 1H), 3.68 (d, J = 4.5 Hz, 4H), 3.31 (q, J = 6.2 Hz, 2H), 3.07 (ddd, J = 9.8, 6.5, 4.2 Hz, 2H), 2.62–2.52 (m, 2H), 2.44 (dd, J = 6.3, 3.4 Hz, 6H), 2.22–2.11 (m, 2H), 1.84–1.60 (m, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 177.74, 161.24, 77.89, 67.18, 57.68, 55.88, 53.55, 37.17, 35.84, 26.37 ppm. FTIR (neat) ν = 3326, 2956, 2856, 2811, 1657, 1512, 1118 cm^{-1}. HR-MS (ESI): $C_{14}H_{26}N_3O_2^+$ $[M+H]^+$: calculated: 268.2020 found: 268.2023.

_N_-(4-Hydroxyphenethyl)tetrahydro-1_H_-pyrrolizine-7a(5_H_)-carboxamide (20)

The reaction was performed using the general procedure on a 0.145 mmol scale. Purification by column chromatography on silica gel using CH_2Cl_2:MeOH = 20:1 (R_f = 0.05). The product was obtained as a white solid in 51 % yield (16 mg, 74 µmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.11 (s, 1H), 7.04–6.96 (m, 2H), 6.78 (dd, J = 8.4, 1.6 Hz, 2H), 3.48 (q, J = 6.6 Hz, 2H), 2.96 (dt, J = 10.3, 5.8 Hz, 2H), 2.72 (t, J = 6.8 Hz, 2H), 2.51 (ddd, J = 9.8, 7.8, 5.6 Hz, 2H), 2.11–2.01 (m, 2H), 1.70 (m, 4H), 1.59–1.44 (m, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 178.12, 155.40, 129.80, 115.56, 77.80, 55.81, 40.27, 37.07, 35.10, 29.84, 26.12 ppm. FTIR (neat) ν = 3279, 2922, 2867, 1640, 1513, 1451, 1241 cm^{-1}. HR-MS (ESI): $C_{16}H_{23}N_2O_2^+$ $[M+H]^+$: calculated: 275.1754 found: 275.1755. M.p. = 109–111°C.

_N_-benzyltetrahydro-1_H_-pyrrolizine-7a(5_H_)-carboxamide (21)

Purification by column chromatography on basic aluminium oxide using EtOAC:pentane = 1:3 (R_f = 0.4). The product was obtained as a yellow oil in 71% yield (82 mg, 0.34 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.32 (s, 1H), 7.38–7.23 (m, 5H), 4.42 (d, J = 6.0 Hz, 2H), 3.10–3.00 (m, 2H), 2.63–2.52 (m, 2H), 2.29–2.20 (m, 2H), 1.86–1.72 (m, 4H), 1.73–1.64 (m, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 177.72, 139.15, 128.74, 127.50, 127.31, 77.96, 55.94, 43.15, 37.35, 26.41 ppm. FTIR (neat) ν = 3322, 2961, 2868, 2362, 1667, 1508 cm^{-1}. HR-MS (ESI): $C_{15}H_{21}N_2O^+$ $[M+H]^+$: calculated: 245.1648 found: 245.1651.

(_S_)-_N_-(1-Phenylethyl)tetrahydro-1_H_-pyrrolizine-7a(5_H_)-carboxamide (22)

Purification by column chromatography on silica gel using CH_2Cl_2:MeOH = 20:1 (R_f = 0.07). The product was obtained as a yellow oil in 69 % yield (69 mg, 0.33 mmol, e.r. 99:1 by HPLC). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.30 (d, J = 6.7 Hz, 1H), 7.37–7.20 (m, 5H), 5.06 (dq, J = 13.9, 6.9 Hz, 1H), 3.14–3.01 (m, 2H), 2.64–2.53 (m, 2H), 2.28–2.20 (m, 1H), 2.19–2.11 (m, 1H), 1.85–1.63 (m, 6H), 1.47 (t, J = 6.3 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 176.69, 144.08, 128.67, 127.10,

126.04, 77.88, 55.95, 47.98, 37.21, 37.19, 26.40, 22.47 ppm. FTIR (neat) ν = 3313, 2965, 2868, 2361, 1669, 1497 cm^{-1}. HR-MS (ESI): $C_{16}H_{23}N_2O^+$ $[M+H]^+$: calculated: 259.1805 found: 259.1805. $[\alpha]^{24}_D$ = -39.3° (*c* = 1.12, $CHCl_3$). Enantiomeric purity was determined by HPLC using a Chiracel 1A column (1 $mLmin^{-1}$, *i*PrOH:*n*-hexane 3:97, UV 225 nm): major enantiomer: t_R = 19.66 min, minor enantiomer t_R = 26.93 min.

Methyl-(hexahydro-1*H*-pyrrolizine-7a-carbonyl)-tryptophanate (23)

The reaction was performed using the general procedure on a 0.3 mmol scale. Purification by column chromatography on silica gel using EtOAc:pentane = 3:1 (R_f = 0.04). The product was obtained as a colorless oil in 77 % yield (82 mg, 0.23 mmol , e.r. 53:47 by HPLC of the Boc-protected derivative). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.46 (d, *J* = 8.6 Hz, 1H), 8.31 (s, 1H), 7.57 (d, *J* = 7.8 Hz, 1H), 7.34 (d, *J* = 8.1 Hz, 1H), 7.20–7.14 (m, 1H), 7.12–7.08 (m, 1H), 6.99 (d, *J* = 2.3 Hz, 1H), 4.87 (dt, *J* = 8.8, 6.1 Hz, 1H), 3.68 (s, 3H), 3.31–3.27 (m, 2H), 3.01–2.95 (m, 1H), 2.82–2.76 (m, 1H), 2.50–2.40 (m, 2H), 2.20–2.12 (m, 1H), 2.05–1.97 (m, 1H), 1.75—1.69 (m, 1H), 1.69–1.62 (m, 4H), 1.40 (m, 1H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 197.26, 182.60, 177.84, 172.79, 136.20, 127.83, 122.62, 122.19, 119.57, 118.75, 111.26, 110.69, 77.73, 55.82, 55.64, 52.77, 52.32, 37.27, 36.89, 27.87, 26.28, 26.21 ppm. FTIR (neat) ν = 3261, 2957, 2923, 2852, 1744, 1646, 1506 cm^{-1}. HR-MS (ESI): $C_{20}H_{26}N_3O_3^+$ $[M+H]^+$: calculated: 356.1969 found: 356.1972. The e.r. was determined by HPLC using a Chiracel OD-H column (0.5 $mLmin^{-1}$, *i*PrOH:*n*-hexane 3:97, UV 225 nm): first enantiomer: t_R = 41.83 min, second enantiomer t_R = 61.73 min.

Methyl-(hexahydro-1*H*-pyrrolizine-7a-carbonyl)-valinate (24)

Purification by column chromatography on silica gel using EtOAc:pentane = 1:1 (R_f = 0.05). The product was obtained as a colorless oil in 69 % yield (55 mg, 0.26 mmol, e.r. 50:50 by HPLC). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.48 (d, *J* = 8.9 Hz, 1H), 4.45 (dd, *J* = 9.6, 4.9 Hz, 1H), 3.71 (s, 3H), 3.19–3.08 (m, 2H), 2.65–2.56 (m, 2H), 2.23–2.13 (m, 3H), 1.83–1.69 (m, 6H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.88 (d, *J* = 6.9 Hz, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 177.80, 172.78, 77.95, 56.76, 55.88, 55.86, 52.11, 37.33, 37.14, 31.21, 26.57, 26.42, 19.38, 17.75 ppm. FTIR (neat) ν = 3322, 2961, 2932, 2870, 1741, 1673, 1499 cm^{-1}. HR-MS (ESI): $C_{15}H_{25}N_2O_5^+$ $[M+H]^+$: calculated: 269.1860 found: 269.1861. The e.r. was determined by HPLC using a Chiracel AD-H column (0.5 $mLmin^{-1}$, *i*PrOH:*n*-hexane 5:95, UV 225 nm): first enantiomer: t_R = 16.73 min, second enantiomer t_R = 20.13 min.

Methyl-(hexahydro-1*H*-pyrrolizine-7a-carbonyl)-phenylalaninate (25)

Purification by column chromatography on silica gel using CH_2Cl_2:MeOH = 40:1 (R_f = 0.48). The product was obtained as a yellow oil in 63 % yield (94 mg, 0.3 mmol, e.r. 53:47 by HPLC). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.38 (d, *J* = 7.6 Hz, 1H), 7.35–7.18 (m, 3H), 7.17–7.08 (m, 2H), 4.85–4.75 (m, 1H), 3.72 (s, 3H), 3.18 (dd, *J* = 13.9, 5.5 Hz, 1H), 3.10–3.04 (m, 1H), 3.03 (dd, *J* = 13.9, 7.6 Hz, 1H), 2.98–2.88 (m, 1H), 2.57–2.46 (m, 2H), 2.19–2.13 (m, 1H), 2.01–1.93 (m, 1H), 1.76–1.71 (m, 1H), 1.70–1.63 (m, 4H), 1.51–1.40 (m, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 172.40, 136.49, 129.35, 128.54, 127.07, 77.81, 55.85, 55.73, 52.73, 52.33, 38.19, 37.12, 36.97, 26.33, 26.23 ppm. FTIR (neat) ν = 3310, 2955, 2869, 1744, 1669, 1502 cm^{-1}. HR-MS (ESI): $C_{18}H_{25}N_2O_3^+$ $[M+H]^+$: calculated: 317.1860 found: 317.1865. The e.r. was determined by HPLC using a Chiracel OD-H column (0.5 $mLmin^{-1}$, *i*PrOH:*n*-hexane 3:97, UV 225 nm): first enantiomer: t_R = 48.25 min, second enantiomer t_R = 58.35 min.

Methyl-(hexahydro-1*H*-pyrrolizine-7a-carbonyl)-methioninate (26)

Purification by column chromatography on silica gel using CH_2Cl_2:MeOH = 20:1 (R_f = 0.38). The product was obtained as a yellow oil in 63 % yield (89 mg, 0.3 mmol, e.r. 52:48 by HPLC). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.49 (d, *J* = 9.1 Hz, 1H), 4.63 (td, *J* = 8.3, 5.0 Hz, 1H), 3.73 (s, 3H), 3.19–3.06 (m, 2H), 2.65–2.56 (m, 2H), 2.52–2.46 (m, 2H), 2.24–2.12 (m, 3H), 2.10 (s, 3H), 2.02–1.91 (m, 1H), 1.88–1.78 (m, 2H), 1.78–1.63 (m, 4H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 177.80, 172.53, 77.70, 55.77, 55.76, 52.34, 51.09, 37.07, 31.98, 30.24, 26.41, 26.24, 15.56 ppm. FTIR (neat) ν = 3305, 2960, 2868, 1743, 1670, 1502, 1442, 1224, 1175 cm^{-1}. HR-MS (ESI): $C_{14}H_{25}N_2O_3S^+$ $[M+H]^+$: calculated: 301.1580 found: 301.1585. The e.r. was determined by HPLC using a Chiracel AD-H column (0.5 $mLmin^{-1}$, *i*PrOH:*n*-hexane 5:95, UV 225 nm): first enantiomer: t_R = 37.20 min, second enantiomer t_R = 42.95 min.

Dimethyl-(hexahydro-1*H*-pyrrolizine-7a-carbonyl)-glutamate (27)

The reaction was performed using the general procedure on a 0.3 mmol scale. Purification by column chromatography on silica gel using EtOAc:pentane = 2:1 (R_f = 0.05). The product was obtained as a yellow oil in 51 % yield (47 mg, 0.15 mmol , e.r. 57:43 by HPLC). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.44 (d, *J* = 8.7 Hz, 1H), 4.53 (td, *J* = 8.8, 5.2 Hz, 1H), 3.72 (s, 3H), 3.67 (s, 3H), 3.17–3.07 (m, 2H), 2.63–2.55 (m, 2H), 2.43–2.29 (m, 2H), 2.27–2.20 (m, 1H), 2.20–2.11 (m, 2H), 2.01–1.92 (m, 1H), 1.81–1.64 (m, 6H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 178.14, 173.14, 172.56, 77.80, 55.89, 55.84, 52.48, 51.92, 51.25, 37.22, 37.18, 30.36, 27.58, 26.46, 26.33 ppm. FTIR (neat) ν = 3261, 2957, 2923, 2852, 1744, 1646, 1506, 1439 cm^{-1}. HR-MS (ESI): $C_{15}H_{25}N_2O_5^+$ $[M+H]^+$: calculated: 313.1758 found: 313.1762. The e.r. was determined by HPLC using a Chiracel AD-H column (0.5 $mLmin^{-1}$, *i*PrOH:*n*-hexane 5:95, UV 225 nm): first enantiomer: t_R = 63.66 min, second enantiomer t_R = 67.22 min.

2-(3-methylbut-2-en-1-yl)-*N*-phenylpyrrolidine-2-carboxamide ($\Delta^{2,3}$) and 2-(3-methylbut-3-en-1-yl)-*N*-phenylpyrrolidine-2-carboxamide ($\Delta^{3,4}$) (30 and 31)

Imine (44 mg, 0.28 mmol, 1.00 equiv.) and isonitrile (29 mg, 0.28 mmol, 1.00 equiv.) were dissolved in dry toluene (2 mL) and $Et_3N{\cdot}HCl$ (77 mg, 0.56 mmol, 2.00 equiv.) was added. The suspension was heated under reflux for 17 h and the reaction was monitored by TLC. The reaction mixture was diluted with water, the layers were separated and the aqueous layer was extracted using EtOAc (2x). The combined organic layers were dried over $MgSO_4$. The solvents were removed in vacuo and the residue was purified by flash column chromatography on silica gel using CH_2Cl_2:MeOH 40:1, 0.1% Et_3N (R_f = 0.24). The two products ($\Delta^{2,3}$:$\Delta^{3,4}$ = 2.1 :1) were obtained as a yellow oil in 57% yield (41 mg, 0.16 mmol).

$\Delta^{2,3}$: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.06 (bs, *J* = 12.0 Hz, 1H), 7.66-7.58 (m, 2H), 7.37-7.27 (m, 2H), 7.12-7.04 (m, 1H), 5.09 (tdt, *J* = 6.8, 2.9, 1.4 Hz, 1H), 3.16-3.03 (m, 1H), 2.99-2.89 (m, 1H), 2.79-2.67 (m, 1H), 2.44-2.32 (m, 1H), 2.28-2.20 (m, 1H), 1.86 – 1.73 (m, 3H), 1.68 (d, *J* = 27.2 Hz, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 175.51, 138.28, 136.37, 129.04, 123.85, 119.29, 118.78, 70.12, 47.34, 36.73, 36.14, 26.56, 26.18, 18.14 ppm.

$\Delta^{3,4}$: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.06 (bs, *J* = 12.0 Hz, 1H), 7.66-7.58 (m, 2H), 7.37-7.27 (m, 2H), 7.12-7.04 (m, 1H), 4.73-4.65 (m, 2H), 3.16-3.03 (m, 1H), 2.99-2.89 (m, 1H), 2.44-2.32 (m, 1H), 2.28-2.20 (m, 1H), 2.02 (td, *J* = 9.8, 5.4 Hz, 2H), 1.86 – 1.73 (m, 4H), 1.72 – 1.70 (m, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 175.01, 145.29, 138.15, 129.07, 123.96, 119.32, 110.33, 70.50, 47.34, 37.39, 37.21, 33.20, 26.33, 22.75 ppm. FTIR (neat) ν = 3244, 2967, 2872, 1681, 1600, 1516, 1441, 1310, 755 cm^{-1}. HR-MS (ESI): $C_{16}H_{23}N_2O^+$ $[M+H]^+$: calculated: 259.1805 found: 259.1809.

3-Oxo-*N*-phenyltetrahydro-1*H*-pyrrolizine-7a(5*H*)-carboxamide (32)

Pyrrolizidine **18** (15 mg, 65 µmol, 1.00 equiv.) was dissolved in anhydrous CH_2Cl_2 (1.0 mL) under argon atmosphere. Benzyl(triethyl)ammonium permanganate (61 mg, 0.195 mmol, 3.00 equiv.) was added and the suspension was stirred for 24 h at room temperature. Conversion was monitored by GC-MS. The suspension was filtered over cotton and the filtrate was transferred to a separation funnel. The solution was washed with water, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2x). The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated. The crude extracts were purified by column chromatography on silica gel using CH_2Cl_2:MeOH = 30:1 (R_f = 0.2). The product was obtained as a white solid in 73% yield (11.6 mg, 47 µmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.15 (s, 1H), 7.62 –7.54 (m, 2H), 7.40–7.31 (m, 2H), 7.19–7.12 (m, 1H), 3.86–3.75 (m, 1H), 3.21 (ddt, *J* = 12.3, 8.3, 4.5 Hz, 1H), 2.82 (dt, *J* = 17.1, 10.2 Hz, 1H), 2.68–2.57 (m, 2H), 2.50 (ddd, *J* = 17.1, 9.5, 2.4 Hz, 1H), 2.30–2.16 (m, 1H), 2.12–1.94 (m, 2H), 1.82–1.70 (m, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 179.17, 172.36, 137.18, 129.27, 125.11, 120.05, 75.23, 43.92, 36.60, 33.58, 32.23, 26.02 ppm. FTIR (neat) ν = 3293, 2953, 1676, 1598, 1532, 1441 cm^{-1}. HR-MS (ESI): $C_{14}H_{17}N_2O_2^+$ $[M+H]^+$: calculated: 245.1285 found: 245.1281. M.p. = 172°C.

7a-(Phenylcarbamoyl)hexahydropyrrolizine-4(1*H*)-oxide (33)

To a solution of pyrrolizidine **18** (10 mg, 43 µmol, 1.00 equiv.) in anhydrous CH_2Cl_2 (0.22 mL) at 0°C was added a solution of *m*-CPBA (12 mg, 43 µmol, 1.00 equiv.) in anhydrous CH_2Cl_2 (0.22 mL). The solution was stirred at 0°C and completion was monitored on TLC (CH_2Cl_2:MeOH = 40:1). After 5 h, the reaction mixture was quenched with sat. aqueous Na_2CO_3 solution. The mixture was diluted with Et_2O and transferred to a separation funnel. The organic layer was washed with Na_2CO_3 solution, the layers were separated and the organic layer was dried over $MgSO_4$. The crude extracts were purified by column chromatography on basic aluminum oxide using CH_2Cl_2:MeOH 100:1 as an eluent (R_f = 0.16). The product was obtained as a colorless oil in 82% yield (8.8 mg, 36 µmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 14.60 (s, 1H), 7.62 (dd, *J* = 8.2, 1.1 Hz, 2H), 7.35–7.25 (m, 2H), 7.07 (td, *J* = 7.3, 1.2 Hz, 1H), 3.87–3.76 (m, 2H), 3.76–3.66 (m, 2H), 2.97–2.86 (m, 2H), 2.38–2.25 (m, 2H), 2.18–2.00 (m, 4H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.96, 138.52, 128.98, 124.09, 120.43, 83.53, 68.40, 32.97, 19.87 ppm. FTIR (neat) ν = 3386, 3270, 2922, 1661, 1596, 1556, 1495, 1449 cm^{-1}. HR-MS (ESI): $C_{14}H_{19}N_2O_2^+$ $[M+H]^+$: calculated: 247.1441 found: 247.1444.

***N*-((Tetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methyl)aniline (34)**

In a two-neck roundbottom flask equipped with a reflux condenser, pyrrolizidine **18** (65 mg, 0.28 mmol, 1 equiv.) in toluene (3 mL) was dissolved under argon and the solution was cooled to 0°C. Red-Al®-solution (0.73 mL, 2.26 mmol, 60% in toluene) was added dropwise. The cooling bath was removed after addition and the reaction mixture was heated to reflux for 15 h. The reaction mixture was cooled to 0°C and aqueous NaOH (c = 3 mol·L^{-1}, 6.5 mL) was added carefully. The reaction mixture was stirred at room temperature overnight. The reaction mixture was transferred into a separation funnel and diluted with ether. The aqueous layer was separated and the organic layer was washed with 10% NaOH solution and brine. The organic layer was dried over $MgSO_4$ and the solvent was evaporated to give the product as a pale yellow oil in 99% yield (60.7 mg, 0.28 mmol). ^{1}H NMR (400 MHz, methanol-d_4) δ = 7.12–7.05 (m, 2H), 6.67–6.62 (m, 2H), 6.62–6.57 (m, 1H), 3.07–3.00 (m, 2H), 3.03 (s, 2H), 2.74–2.66 (m, 2H), 2.00–1.93 (m, 2H), 1.92–1.85 (m, 2H), 1.82–1.74 (m, 2H), 1.72–1.66 (m, 2H) ppm. ^{13}C NMR (101 MHz, methanol-d_4) δ = 150.68,

130.03, 117.94, 113.83, 56.41, 53.52, 37.32, 25.77 ppm. FTIR (neat) ν = 3360, 2953, 2865, 2357, 1604, 1504, 1315, 1260 cm^{-1}. HR-MS (ESI): $C_{14}H_{21}N_2^+$ $[M+H]^+$: calculated: 217.1699 found 217.1703.

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